Cerebral oxygen balance is impaired during repair of aortic coarctation in infants and children

Anthony Azakie, MD,[a]* Jessica Muse, BS,[c]* Marisa Gardner, BS,[c] Kimberly L. Skidmore, MD,[b] Steven P. Miller, MD,[c] Tom R. Karl, MD,[a] and Patrick S. McQuillen, MD[d]

Objective: During repair of aortic coarctation through a left thoracotomy without cardiopulmonary bypass, clamping the proximal transverse aortic arch occludes antegrade flow to the left carotid and vertebral arteries. It is assumed that flow through the right carotid and vertebral arteries is adequate for cerebral perfusion. The study objective is to determine whether aortic occlusion impairs left hemispheric cerebral oxygen balance measured by near-infrared spectroscopy.

Methods: In 18 children having repair of aortic coarctation, we measured the maximum change and integral for hemoglobin D (difference of oxyhemoglobin and deoxyhemoglobin), total oxygenation index, and the redox state of cytochrome aa3. Thirteen subjects had recordings from the left hemisphere to test the hypothesis that aortic occlusion impairs left hemispheric oxygen balance. Five subjects had recordings from the right hemisphere for comparison.

Results: After aortic clamping, a significant decrease in hemoglobin D was observed in recordings from the left hemisphere compared with those from the right hemisphere ($P = .03$, maximum change in hemoglobin D). Total oxygenation index and cytochrome aa3 were generally preserved. There was an inverse linear relationship for the change in hemoglobin D during clamp application and after removal (Spearman rho $= -0.74$), with increased hemoglobin D after clamp removal in those subjects with the greatest decrease of hemoglobin D during arch occlusion. Linear regression analysis identified nitroprusside administration as significantly associated with a decrease in hemoglobin D ($P < .001$).

Conclusions: Significant impairment in left hemispheric cerebral oxygen balance was identified during arch clamping. The neurodevelopmental significance of impaired cerebral oxygen balance detected by near-infrared spectroscopy during aortic coarctation repair remains to be elucidated.

Because modern surgical techniques to repair congenital heart defects have reduced subsequent cardiac-related mortality and morbidity, focus has turned toward optimizing neurodevelopmental outcome. Repair of isolated aortic coarctation is a procedure with low morbidity and favorable results.[1] Neurodevelopmental outcome has not been selectively examined in this patient population, although neonatal subjects with aortic coarctation have been included in larger studies assessing neurodevelopmental outcome in infants with congenital heart disease.[2,3] These studies find that, as a group, neonates with congenital heart disease perform within population norms when assessed later in life.[3] However, in comparative studies children with congenital heart disease perform consistently lower than reference populations.[3,4] One risk factor for cerebral injury and poor neurodevelopmental outcome is intraoperative cerebral ischemia,[5,6] which can occur during aortic occlusion required for repair of aortic coarctation. Typically, but depending on arch anatomy and repair technique, the clamp occludes blood flow to the left

From the Departments of Surgery,[a] Anesthesia,[b] Neurology,[c] and Pediatrics,[d] University of California, San Francisco, Calif.

This work was supported by the UCSF School of Medicine Dean's Summer Research Fellowship (J.M.) and the American Heart Association Undergraduate Student Research Program (M.G.). A UCSF School of Medicine Dean's Office Research Evaluation and Allocation Committee shared equipment grant (P.M.) was used to purchase the Hamamatsu NIRO-300.

Presented at Scientific Sessions of the American Heart Association, New Orleans, La, 2004.

Received for publication Feb 23, 2005; revisions received April 1, 2005; accepted for publication April 12, 2005.

Address for reprints: Patrick McQuillen, MD, 505 Parnassus Ave, Room M680, San Francisco, CA 94143-0106 (E-mail: psmcq@itsa.ucsf.edu).

*These authors contributed equally to this work.

J Thorac Cardiovasc Surg 2005;130:830-6

0022-5223/$30.00

doi:10.1016/j.jtcvs.2005.04.015

CHD

subclavian and vertebral arteries and possibly to the left carotid artery. In the latter case, blood flow to the left hemisphere must be provided through collateral circulation around the circle of Willis. However, abnormalities of the circle of Willis are common in the general population, with a complete circle of Willis being the exception (21%) rather than the rule.[7] In fact, in one study of healthy young adults, magnetic resonance angiography revealed an entirely incomplete (anterior and posterior) circle of Willis in 6%.[8]

Near-infrared spectroscopy (NIRS) is a noninvasive optical method that measures changes in tissue chromophore concentration[9,10] that correlate with cerebral blood flow,[11] oxygenation,[10] and cellular energetics,[12] which allow an estimation of the balance of cerebral oxygen delivery and use. The objective of this study was to measure cerebral oxygenation with NIRS during aortic clamping to determine whether cerebral oxygen balance is impaired.

Methods

Children undergoing repair of coarctation of the aorta through a left thoracotomy without the use of cardiopulmonary bypass between February 2003 and June 2004 were prospectively studied. Subjects with additional congenital heart defects or extracardiac anomalies were excluded. The Institutional Committee on Human Research at the University of California, San Francisco Children's Hospital, approved this observational study.

NIRS

NIRS measurements were performed with a NIRO-300 (Hamamatsu Photonics, Hamamatsu City, Japan) equipped with a single monitoring unit. This limitation precluded simultaneous recording from the right and left hemispheres. Therefore, each subject was recorded from either the left hemisphere or the right hemisphere to determine the effects both distal (left hemisphere) and proximal (right hemisphere) to the aortic clamp. Recordings were obtained from the left hemisphere in the first 13 subjects and from the right hemisphere in the subsequent 5 subjects as a comparison group. Each recording was started before aortic clamp application and continued after release of the clamp, allowing comparison of NIRS variables both during clamping and after release within and between left and right hemisphere groups.

Immediately after induction of anesthesia, the NIRS probe was applied to the skin of the forehead below the hairline. The probe consists of a transmitting optode emitting 4 infrared wavelengths and an array of 3 photodiode detectors separated by a fixed distance of 4 cm in a probe holder. The NIRO-300 monitoring unit measures relative change in the concentration of oxygenated and deoxygenated hemoglobin and cytochrome aa3 (CytOx). The array of photodiode detectors allows calculation of an absolute value for total oxygenation index (TOI) by the method of spatially resolved spectroscopy.[13] Continuous measurement of NIRS values with a sample rate of 1 second were digitally recorded, along with patient physiologic variables (heart rate, blood pressure, electrocardiographic, and pulse oximetry), onto a portable computer (Dell Inc, Round Rock, Tex) running BioBench software (National Instruments, Temecula, Calif). Patient data, including hematocrit value, core body temperature, and vasoactive medications, were recorded from the anesthesia record. From NIRS measurements, hemoglobin difference (HbD; $HbD = O_2Hb - HHb$), a measure of cerebral blood flow,[11] was derived. Absolute values of the primary NIRS variables are reported as micromoles per liter times the differential pathlength factor, a value that might vary between NIRS measurements. Therefore, a baseline was calculated as the average NIRS value for 5 minutes before application and removal of the aortic clamp, and only measures of the relative change in NIRS variables were analyzed. Specifically, during aortic clamping and after removal of the clamp, the maximum change and integral from baseline throughout the period (Figure 1) were calculated for HbD, TOI, and CytOx by BioBench software.

Anesthetic and Surgical Management

Subjects in this cohort underwent anesthesia according to a uniform clinical practice at our institution that includes induction with sevoforane and pancuronium and maintenance with sevoforane, fentanyl, and midazolam. Subjects were intubated and positioned in a lateral recumbent position for left thoracotomy. The aortic arch, arch branches, and descending aorta were dissected and mobilized. The ductus arterious was dissected and ligated. Proximal control was achieved between the innominate and left carotid arteries ($n = 13$) or between the left carotid artery and left subclavian artery ($n = 5$). The descending aorta was controlled with an angled vascular clamp distal to the coarctation. No intercostal arteries were sacrificed. In a minority of patients, synthetic patch ($n = 2$) or subclavian arterial augmentation ($n = 1$) of the coarctation site and adjacent arch was performed. In most patients, the favored approach was to perform an extended end-to-end ($n = 10$) or end-to-side anastomosis ($n = 5$): the coarctation was excised along with all ductal tissue that extended into the aorta. The undersurface of the aortic arch was incised, and an extended end-to-end or end-to-side anastomosis was completed with running 7-0 polypropylene sutures. The clamps were slowly removed. Fourteen of 18 patients had proximal arch control between the innominate artery and the left common carotid artery. Of these patients, 13 had left-sided NIRS monitoring. Of the 5 children who had right-sided NIRS monitoring, 4 had proximal control distal to the left common carotid artery, and the other had arch clamping proximal to the left common carotid artery.

Data Analysis

Processed NIRS and physiologic data and patient information recorded manually were inserted into a common database for statistical analysis with Stata software (Stata Corp, College Station, Tex). The maximum change and integral (Figure 1) for HgD, TOI, and CytOx of recordings from the right and left forehead during and after aortic clamping were compared by using the Mann-Whitney U test for continuous or ordinal data. Nominal data were compared with the Fisher exact test. Linear regression (univariate) was used to assess the relationships between the changes in each NIRS variable with patient (age, weight, sex, and coarctation type), pharmacologic (use of antihypertensive or inotropic medications), or operative (aortic crossclamp time and surgical procedure) characteristics.

CHD

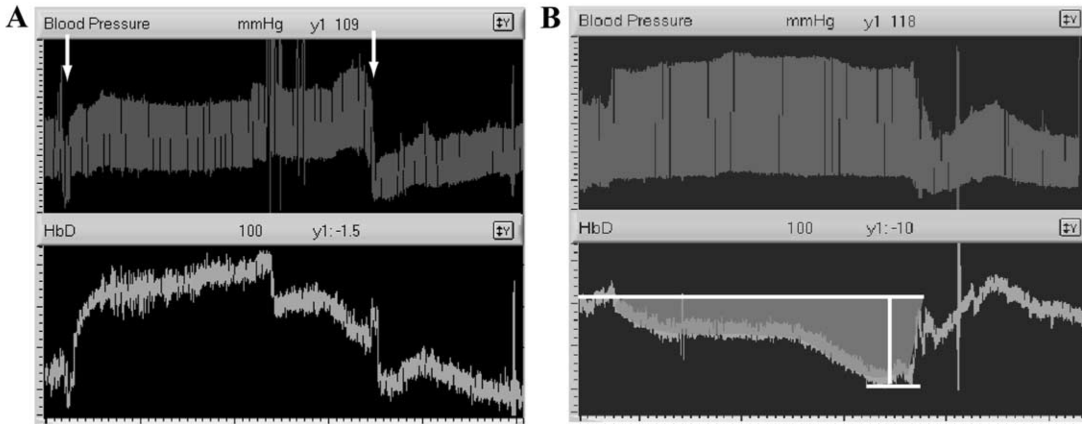

Figure 1. Right radial arterial blood pressure and NIRS recordings derived from both the right (A) and left (B) cerebral hemispheres of infants undergoing coarctation repair. The upper tracings of both A and B show blood pressure *(vertical axis)*, and the lower tracings show change in HbD *(vertical axis)* over time *(horizontal axis)*. The first *arrow* depicts application of the aortic clamp; the second *arrow* indicates declamping of the aorta. B, The lower tracing illustrates 2 measurements derived from NIRS recordings: (1) maximum change in HbD (difference between *horizontal white lines*) and (2) integral of HbD (*gray, shaded area* above the tracing).

Results

Patient and Procedural Characteristics

We studied 18 subjects aged 1 week to 9 years. Thirteen consecutive subjects had the NIRS probe applied to the left side of the forehead to monitor the effects of aortic clamping on cerebral oxygenation distal to the clamp, and the subsequent 5 subjects had the NIRS probe applied to the right side of the forehead for comparison of cerebral oxygenation proximal to the aortic clamp. Subjects who had recordings from the right hemisphere were older (median, 46.8 months vs 5.2 months) and all were male (left hemisphere subjects, n = 7/13 [54%] male). However, the aortic occlusion time (mean ± SD, 18 ± 5 minutes in the left hemisphere vs 19 ± 2 minutes in the right hemisphere; P = .64, Mann-Whitney test), the frequency of hypoplastic isthmus (n = 3/13 in the left hemisphere vs 3/5 in the right hemisphere; P = .27, Fisher exact test), and the distribution of repair techniques (P = .06, Fisher exact test) were similar. Most patients in this study had coarctation repair with an extended end-to-end (n = 10) or end-to-side (n = 5) anastomosis. Other techniques used included patch augmentation (n = 2) and subclavian flap (n = 1).

Aortic Clamping Decreases Hemoglobin D Levels

Figure 1 presents typical raw data tracings for blood pressure (upper panels) and HgD (lower panels) in subjects monitored over the right hemisphere (Figure 1, *A*) and those monitored over the left hemisphere (Figure 1, *B*). Occlusion of the aorta (*first arrow*; Figure 1, *A*) increases blood pressure proximal to the clamp as the entire cardiac output is delivered to the proximal aorta. After release of aortic clamps (*second arrow;* Figure 1, *A*), there is a transient decrease in blood pressure as the cardiac output is redistributed to the descending aorta before regulation back to baseline. In all 5 subjects monitored over the right hemisphere, HbD increased during aortic clamping (Figures 1, *A*, and 2, *A* and *B*) and transiently decreased after removal of the aortic clamp (Figure 1, *A*, and 2, *A* and *B*). In contrast, 10 of 13 subjects monitored over the left hemisphere had a significant decrease in HbD as measured by maximum change (Figure 1 and 2, *A*; P = .03, Mann-Whitney test) or the integral during aortic clamping (Figures 1 and 2, *B*; P = .03, Mann-Whitney test). Subjects monitored over the left hemisphere showed a more variable response after release of the clamp, with individual subjects showing an increase in HgD with clamp removal (n = 5) and others having a decrease in HgD (n = 8). HgD was not significantly different after clamp removal among subjects measured over the left and right hemispheres (Figure 2, *A*; P = .15, Mann-Whitney test). An inverse linear relationship is observed in the change in HgD with the aortic clamp and removal (Figure 3), with those subjects with the largest decrease in HgD after aortic clamping having an increase in HgD after clamp removal (Spearman rho = −0.74).

Cerebral Oxygenation and Cellular Metabolism Are Generally Preserved During Aortic Clamping

During aortic clamping in subjects monitored over the right hemisphere, cerebral oxygenation measured by TOI increased in all but one patient (Figure 2, *C*). In contrast, subjects monitored over the left hemisphere displayed a more variable response, with the majority of subjects (n =

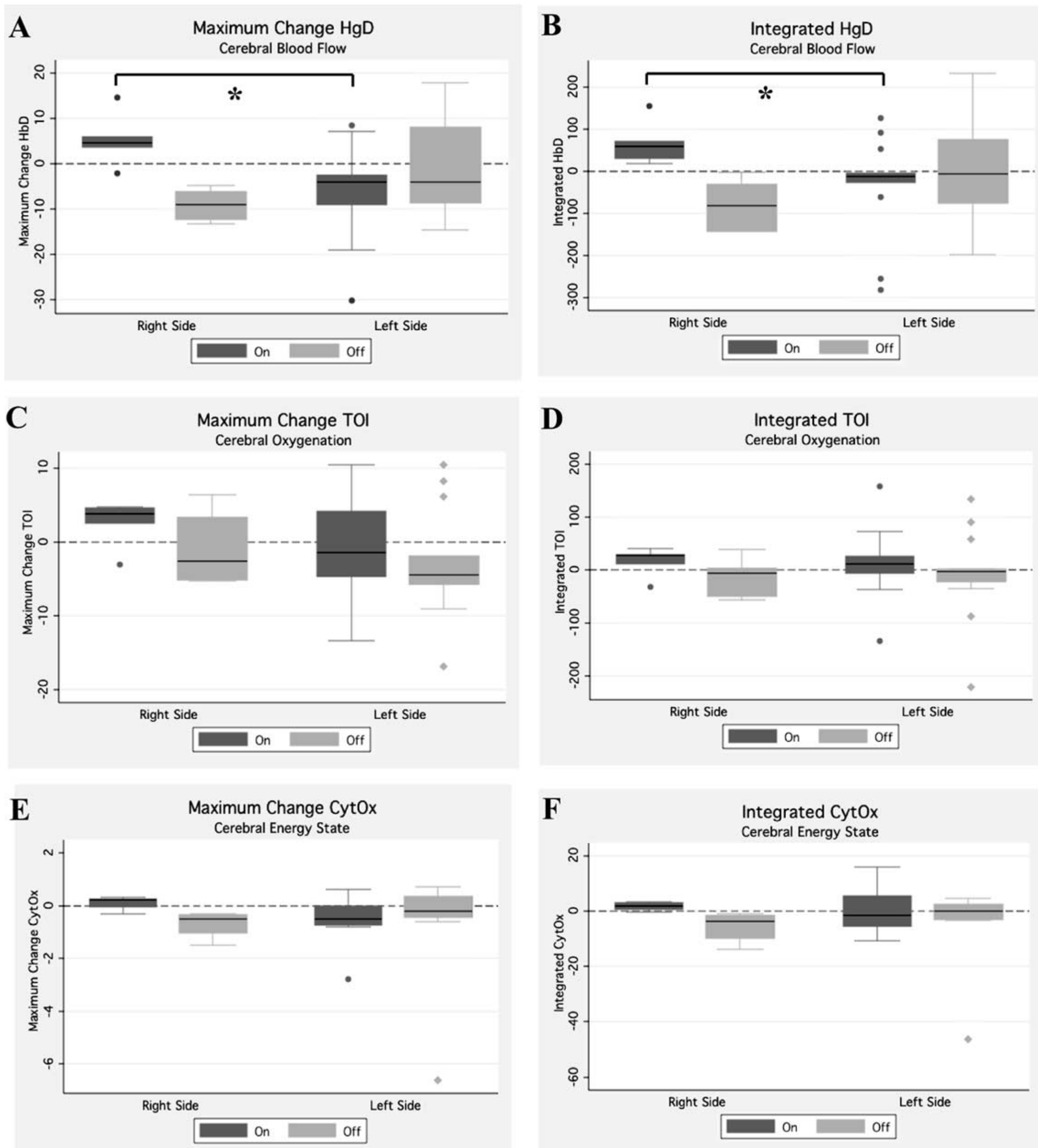

Figure 2. Summary and comparison of NIRS variables from recordings over the right and left cerebral hemispheres during coarctation repair in children. All data are presented as medians and interquartile ranges, with outliers plotted individually. Maximum change in HbD (A) and integrated HbD (B; *vertical axes*), as recorded over both the right and left cerebral hemispheres with application *(dark shading)* and removal *(gray shading)* of aortic clamping, is shown. Cerebral oxygen balance, as measured by both maximum change in HbD and integrated HbD, is significantly lower on the left side compared with the right side on proximal occlusion of the aortic arch. However, indicators of cerebral oxygenation (C and D, maximum change in TOI and integrated TOI [*vertical axes*]) and cerebral cellular oxygen metabolism (E and F, maximum change in CytOx and integrated CytOx [*vertical axes*]) are not significantly different between the right and left sides during clamping and declamping of the aorta.

7) having a negative maximum change in TOI during aortic clamping. However, comparison of the change of TOI during aortic clamping among the left and right hemisphere groups (Figure 2, *C* and *D*) did not identify significant differences ($P = .3$ maximum change; $P = .6$ integral TOI, Mann-Whitney). This observation and the fact that the median integral change of TOI after aortic clamping is slightly positive (Figure 2, *D*) reflects that many subjects monitored

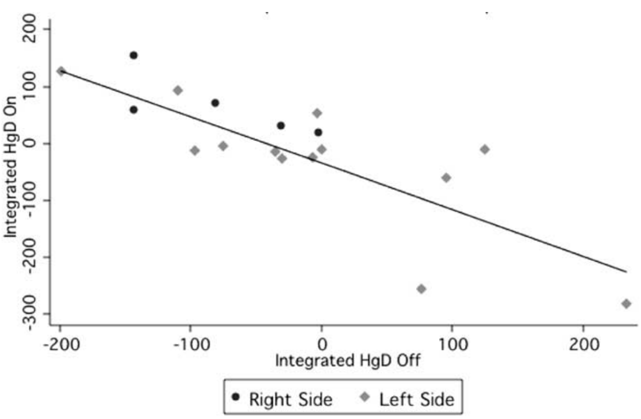

Figure 3. Inverse relationship of change in HbD (integrated) during clamp application and removal.

over the left hemisphere recovered TOI values back to and above baseline by the end of the clamping period.

Similar changes to those in TOI were observed from the subset of subjects monitored over the left hemisphere (n = 8) and subjects monitored over the right hemisphere (n = 4) who had CytOx recorded during their procedure. Only one subject monitored over the right side had a decrease in the maximal change or integral CytOx. However, the majority of subjects with left-sided monitoring (n = 6) had a small decrease (median, −0.2 μmol/L*dpf; range, −2.8 to 0.6) in the maximum change of CytOx during aortic clamping. After clamp removal, all subjects monitored over the right hemisphere had a decrease in maximum change or integral of CytOx. Subjects monitored over the left hemisphere had a variable response of maximum change or integral CytOx after clamp removal. The patient monitored over the left hemisphere with the largest decrease in maximum change for CytOx during clamping (−2.8 μmol/L*dpf) continued to experience a decrease after clamp removal, resulting in the largest observed change in CytOx during the study (−6.6 μmol/L*dpf; Figure 2, *E*).

Nitroprusside Treatment During Aortic Clamping Decreases Cerebral Oxygen Balance

On univariate analysis, the 2 patients treated with nitroprusside during aortic clamping had a significant decrease in HbD (P = .001, maximum change; P < .001 integral; Table 1) and in TOI (P = .04), but not in CytOx. This effect was specific for nitroprusside administered during aortic clamping because nitroprusside administered before or after clamping was not associated with a decrease in HbD (all P > .2, Table 1). In light of this relationship of nitroprusside to cerebral oxygen balance during aortic clamping, we examined the effects of other vasoactive infusions. The effect is unique to nitroprusside because esmolol or inotropes (dopamine and dobutamine) administered at any time did not affect HbD (all P > .1).

Characteristics of the patient, including age and weight, presence of aortic isthmus hypoplasia, procedure used, or time needed to repair the coarctation, were also not associated with changes in cerebral oxygenation measured by means of NIRS (all P > .1). Changes affecting oxygen-carrying capacity (hematocrit) or metabolic rate (patient temperature), which are known to affect NIRS variables, did not account for the changes observed during aortic clamping (all P > .1). Finally, blood pressure measured during clamp application and after removal was not associated with changes in HgD or TOI. However, blood pressure was significantly associated with the integral of CytOx (P = .04, Table 1). This association cannot explain the effect of nitroprusside administered during aortic clamping because nitroprusside administration was not associated with significant changes in CytOx (P = .9, maximum change; P = .1, integral; Table 1).

TABLE 1. Univariate regression analysis of predictors of changes in NIRS variables

Variable		Max Δ HbD		Max Δ TOI		Max Δ CytOx	
		Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
Nitroprusside	Before/after clamping*	−5.1	.33	−5.1	.26	0.2	.90
	During clamping*	*−23.3*	*.001*	*−10.4*	*.04*	−0.1	.91
Max Δ MAP		0.2	.59	0.1	.75	0.0	.60
		Integral HbD		**Integral TOI**		**Integral CytOx**	
		Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
Nitroprusside	Before/after clamping*	−51.8	.24	−40.3	.43	−7.8	.40
	During clamping*	*−287.5*	*<.001*	−84.2	.11	−12.8	.10
Max Δ MAP		4.7	.28	1.9	.44	*1.1*	*.04*

Statistically significant values are shown in italics. *HbD,* Hemoglobin difference; *TOI,* total oxygenation index; *CytOx,* cytochrome aa3; *MAP,* mean arterial pressure. *Nitroprusside before/after clamping (n = 2); nitroprusside during clamping (n = 2).

Clinical Outcomes and Follow-up

There were no hospital deaths, and all children are alive at a median follow-up of 15 months. No patients have required balloon dilation for recoarctation.

Discussion

Neurologic complications of heart surgery in infants and children are common, with a reported incidence of 2.3% for overt clinical presentation[14] and up to 54% to 67% when more sensitive magnetic resonance imaging is applied.[15,16] Successful prevention of cerebral injury requires closer investigation of the timing and mechanisms of acquired injury.[16,17] NIRS monitoring during cardiac surgery offers several distinct advantages. NIRS is portable, noninvasive, continuous, and relatively inexpensive. Selected NIRS variables can be measured to estimate cerebral blood flow (HgD),[11] cerebral oxygenation (TOI),[13] and intracellular energetics (CytOx),[12] which reflect brain function. In this study we have used NIRS to monitor cerebral oxygen balance during aortic occlusion for repair of aortic coarctation through a left thoracotomy without the use of cardiopulmonary bypass.

Repair of coarctation of the aorta with or without arch hypoplasia requires extensive mobilization of arch vessels, the descending aorta, and intercostal branches. All ductal tissue is excised, and a large tension-free anastomosis to the undersurface of the aorta can be accomplished to prevent recoarctation, especially in neonates with transverse arch hypoplasia. Such an operative strategy usually requires control of the arch proximal to the left carotid artery, just distal to the innominate artery, or both. This assumes that collateral blood flow and completeness of the circle of Willis allows for a favorable and even distribution of cerebral blood flow.

Here we show that in a significant subset of patients undergoing coarctation repair, proximal occlusion of the aortic arch results in transient but significant impairment in contralateral cerebral oxygen balance. Monitoring of NIRS variables proximal to the aortic clamp (right side) consistently showed that on aortic arch occlusion, HbD, an indirect marker of cerebral blood flow, increased. On removal of the clamp, right-sided HbD decreased to baseline levels. However, NIRS monitoring distal to the aortic clamp (left side) showed that on application of the arch clamp, a progressive decrease in left-sided HbD occurred, despite increases in right radial arterial blood pressure. Nitroprusside use exacerbated the decrease in HbD in 2 patients. Use of nitroprusside to treat hypertension resulted in a 10-fold greater reduction in left-sided cerebral blood flow, as measured on the basis of HbD. Andropoulos and colleagues[18,19] have reported decreased saturation in the left cerebral hemisphere in most patients during regional cerebral perfusion for neonatal aortic arch repair. This group uses phenoxybenzamine for afterload reduction as part of their standard bypass strategy for arch repair. This might explain the high frequency of impaired left cerebral oxygen balance during regional cerebral perfusion if phenoxybenzamine impairs cerebral autoregulation in the same manner that we have observed for nitroprusside.

On completion of the coarctation repair and removal of clamps, HbD decreased because of relative systemic hypotension, except in those patients with the greatest magnitude of decrease during clamping. In these patients HbD increased even in the setting of systemic redistribution of flow after clamp removal, suggesting a left-sided cerebral vasodilatation to compensate for the decreased flow during arch occlusion. Despite decreases in left-sided HbD during proximal arch occlusion, indicators of cerebral oxygenation and cerebral energetics appeared to be preserved.

Rodriguez and associates[20] reported their experience with the cerebral effects of aortic occlusion during coarctation repair in children. Using transcranial Doppler scanning to monitor middle cerebral artery blood velocity, the authors found transient central nervous system hypoperfusion as a consequence of flow redistribution during aortic declamping in young infants. Older children usually showed faster autoregulatory compensation to the hemodynamic changes that occurred after unclamping the aorta. The authors inferred age-related physiologic differences, suggesting that young infants might require higher perfusion pressures during declamping to prevent decreases in cerebral blood flow. In the current study changes in left-sided cerebral oxygen balance during clamp application and early after its removal were not age dependent and were uniformly observed in neonates, infants, and older children. It should be noted, however, that after clamping, the decrease in HbD noted on left-sided NIRS monitoring was not absolute. There was a minority of patients in whom left-sided cerebral oxygen balance did not change during proximal arch occlusion, implying that cerebral autoregulatory mechanisms were active and also suggesting a completeness of the circle of Willis.

This study has notable limitations. The NIRS device used in this study was only capable of monitoring a single site, preventing simultaneous recording proximal and distal to the aortic clamp. HbD and CytOx are only indirect estimates of cerebral blood flow and cellular energetics, respectively. Current NIRS technology only allows for relative measurements of the primary NIRS variables. NIRS monitors use device-specific strategies (eg, spatially resolved spectroscopy) to derive an absolute measure of oxygen saturation.[13] Continuous transcranial Doppler (TCD) insonation of the middle cerebral artery and jugular venous oximetry are alternative techniques that have been used during cardiac surgery to estimate cerebral blood flow. However, TCD measures cerebral blood flow velocity and not flow,[21] and TCD does not monitor oxygen delivery or extraction. Con-

CHD

tinuous jugular venous oximetry, in contrast, can estimate cerebral oxygen extraction but is invasive and insensitive to regional cerebral ischemia.

We did not observe any clinical neurologic sequelae of the NIRS findings of impaired left-sided cerebral oxygen balance during a proximal arch occlusion, which is consistent with the fact that only 2 patients had a maximum decrease in TOI of greater than 10 μmol/L*dpf, a magnitude of decrease[22] that has been associated with postoperative neurologic dysfunction.[23] In particular, there was no evidence of postoperative neurologic deficit, stroke, or seizures, although this cohort was not studied with postoperative magnetic resonance imaging. Therefore, the question remains how to determine the neurodevelopmental effects of transient and asymmetric but significant impairment in cerebral oxygen balance during a coarctation repair. Significant cerebral injury can occur in neonates and can be undetectable by means of clinical examination.[17] Preoperative and postoperative magnetic resonance imaging will now be applied to determine whether brain injury occurs after transient decreases in left-sided cerebral blood flow measured by means of HbD. To avoid impairments in cerebral blood flow, it can be argued that a transsternal approach with relative hypothermia and selective cerebral perfusion might be optimal for children who have coarctation of the aorta, especially with arch hypoplasia. The current data also support the avoidance of afterload reduction to treat right radial arterial hypertension during aortic clamping because normalization of right radial arterial blood pressure can result in significant impairment of cerebral oxygen balance, possibly because of disruption of cerebral autoregulatory mechanisms. Furthermore, as previously reported, flow redistribution and hypotension occurs after declamping of the aorta, and persistent mild descending aortic compression might be indicated after clamp removal to avoid decreases in blood pressure and thus reduction in cerebral blood flow.

In conclusion, we have identified a significant decrease of HbD, a surrogate marker of cerebral blood flow, in the left hemisphere during aortic clamping in selected patients. Ongoing studies with intraoperative NIRS monitoring and postoperative magnetic resonance imaging and neurodevelopmental follow-up are needed.

CHD

References

1. Mavroudis C, Backer CL. Pediatric cardiac surgery. 3rd ed. Philadelphia: Mosby; 2003. p. xv, 875.
2. Dittrich H, Buhrer C, Grimmer I, Dittrich S, Abdul-Khaliq H, Lange PE. Neurodevelopment at 1 year of age in infants with congenital heart disease. *Heart.* 2003;89:436-41.
3. Forbess JM, Visconti KJ, Hancock-Friesen C, Howe RC, Bellinger DC, Jonas RA. Neurodevelopmental outcome after congenital heart surgery: results from an institutional registry. *Circulation.* 2002; 106(suppl I):I95-102.
4. Karl TR, Hall S, Ford G, Kelly EA, Brizard CP, Mee RB, et al. Arterial switch with full-flow cardiopulmonary bypass and limited circulatory arrest: neurodevelopmental outcome. *J Thorac Cardiovasc Surg.* 2004;127:213-22.
5. du Plessis AJ. Mechanisms of brain injury during infant cardiac surgery. *Semin Pediatr Neurol.* 1999;6:32-47.
6. Mahle WT. Neurologic and cognitive outcomes in children with congenital heart disease. *Curr Opin Pediatr.* 2001;13:482-6.
7. Riggs HE, Rupp C. Variation in form of circle of Willis: the relation of the variations to collateral circulation: anatomic analysis. *Arch Neurol.* 1963;8:8-14.
8. Krabbe-Hartkamp MJ, van der Grond J, de Leeuw FE, de Groot JC, Algra A, Hillen B, et al. Circle of Willis: morphologic variation on three-dimensional time-of-flight MR angiograms. *Radiology.* 1998; 207:103-11.
9. Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science.* 1977;198: 1264-7.
10. Madsen PL, Secher NH, Near-infrared oximetry of the brain. *Prog Neurobiol.* 1999;58:541-60.
11. Soul JS, Taylor GA, Wypij D, Duplessis AJ, Volpe JJ. Noninvasive detection of changes in cerebral blood flow by near-infrared spectroscopy in a piglet model of hydrocephalus. *Pediatr Res.* 2000;48:445-9.
12. Tsuji M, Naruse H, Volpe J, Holtzman D. Reduction of cytochrome aa3 measured by near-infrared spectroscopy predicts cerebral energy loss in hypoxic piglets. *Pediatr Res.* 1995;37:253-9.
13. Quaresima V, Sacco S, Totaro R, Ferrari M. Noninvasive measurement of cerebral hemoglobin oxygen saturation using two near infrared spectroscopy approaches. *J Biomed Opt.* 2000;52:201-5.
14. Menasché CC, du Plessis AJ, Wessel DL, Jonas RA, Newburger JW. Current incidence of acute neurologic complications after open-heart operations in children. *Ann Thorac Surg.* 2002;73:1752-8.
15. Galli KK, Zimmerman RA, Jarvik GP, Wernovsky G, Kuypers MK, Clancy RR, et al. Periventricular leukomalacia is common after neonatal cardiac surgery. *J Thorac Cardiovasc Surg.* 2004;127:692-704.
16. Mahle WT, Tavani F, Zimmerman RA, Nicolson SC, Galli KK, Gaynor JW, et al. An MRI study of neurological injury before and after congenital heart surgery. *Circulation.* 2002;106(suppl I):I109-14.
17. Miller SP, McQuillen PS, Vigneron DB, Glidden DV, Barkovich AJ, Ferriero DM, et al. Preoperative brain injury in newborns with transposition of the great arteries. *Ann Thorac Surg.* 2004;77:1698-706.
18. Andropoulos DB, Diaz LK, Fraser CD Jr, McKenzie ED, Stayer SA. Is bilateral monitoring of cerebral oxygen saturation necessary during neonatal aortic arch reconstruction? *Anesth Analg.* 2004;98: 1267-72.
19. Andropoulos DB, Stayer SA, McKenzie ED, Fraser CD Jr. Regional low-flow perfusion provides comparable blood flow and oxygenation to both cerebral hemispheres during neonatal aortic arch reconstruction. *J Thorac Cardiovasc Surg.* 2003;126:1712-7.
20. Rodriguez RA, Weerasena N, Cornel G, Splinter WM, Roberts DJ. Cerebral effects of aortic clamping during coarctation repair in children: a transcranial Doppler study. *Eur J Cardiothorac Surg.* 1998; 13:124-9.
21. Andropoulos DB, Stayer SA, Diaz LK, Ramamoorthy C. Neurological monitoring for congenital heart surgery. *Anesth Analg.* 2004;99:1365-75.
22. Gagnon RE, Macnab AJ, Gagnon FA, Blackstock D, LeBlanc JG. Comparison of two spatially resolved NIRS oxygenation indices. *J Clin Monit Comput.* 2002;17:385-91.
23. Austin EH 3rd, Edmonds HL Jr, Auden SM, Seremet V, Niznik G, Sehic A, et al. Benefit of neurophysiologic monitoring for pediatric cardiac surgery. *J Thorac Cardiovasc Surg.* 1997;114:707-17.